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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/687,951	10/13/2000	Jeffrey I. Cleland	M-9177-US	8871

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EXAMINER
KAM, CHIH MIN

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 05/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/687,951	CLELAND ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17,20-23,25-31 and 33-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17, 20, 21, 23, 25-29, 34 and 35* is/are rejected.

7)☒ Claim(s) *22,30,31,36 and 37* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 17, 20-23, 25-31 and 33-37 are pending.

Applicants' response filed on March 8, 2004 is acknowledged and has been fully considered. Claims 20, 30 and 31 have been amended, and claims 17, 20-23, 25-31 and 33-37 are examined.

Rejection(s) Withdrawn

Claim Rejections - 35 USC § 112

2. The previous rejection of claims 21-31, 33 and 34 under 35 U.S.C. 112, first paragraph, is withdrawn in view of applicant's amendment to the claim and applicants' response at pages 6-7 in the amendment filed March 8, 2004.

3. The previous rejection of claims 20-23, 25-31, 33, 34 and 36 under 35 U.S.C. 112, second paragraph, is withdrawn in view of applicant's amendment to the claim and applicants' response at pages 7-8 in the amendment filed March 8, 2004.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 23 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claim 23 recites the limitation "physiological saline" in line 2. There is insufficient antecedent basis for this limitation in the claim because saline is a NaCl

solution and is not per se a buffer solution, see "a physiological buffer" in claim 21, which requires dissolving in a buffer.

6. Claim 26 is indefinite because the claim has the same scope as claim 25, it appears that the listed claim 26 is not the same as the previous claim 26. Claims 25 and 26 have 100% word identity.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

7. Claims 17, 21, 25-29 and 35 are rejected under 35 U.S.C. 102(b) as being anticipated by McGinity *et al.* (US Patent 5,288,502, February 22, 1994).

McGinity *et al.* teach a preparation of multi-phase polymeric microspheres containing a molecular compound dispersed in a polymeric matrix and having particle

size about 150 microns can be administered intramuscularly (Fig. 1, column 8, lines 48-62), wherein the molecular compound can be a water soluble drug or protein (e.g., epidermal growth factor, LHRH, monoclonal antibody, column 6, lines 21-41; claims 28, 29 and 35) in a microemulsion of a fixed oil and an aqueous solution of microspheres (column 4, line 61-column 5, line 2), a biodegradable polymer such as poly(lactic acid) (PLA) and poly(lactide-co-glycolide) (PLGA) is used as a polymeric matrix (column 6, line 59-column 7, line 2; claims 25-27), and some modification of the preparation of microspheres can be made, e.g., the pH of the aqueous phase containing the water soluble drugs can be adjusted using acid or phosphate buffer and a stabilizing agent such as hyaluronic acid can be added to enhance the stability of the protein (Example 7, claims 17 and 21).

In response, applicants indicates McGinity *et al.* teach the use of hyaluronic acid as a stabilizing agent for multiphase polymeric microspheres, and hyaluronic acid is one of the listed stabilizing agents, and there is no description nor suggestion that hyaluronic acid be included in a physiological buffer of an injectable formulation for injection in smaller needles (pages 8-9 of the response). The response has been fully considered, however, the argument is not found persuasive because the reference indicates the adjustment of pH of the aqueous phase and stabilizing agent for drugs may be necessary in order to enhance the stability of the protein for the multi-phase polymeric microspheres (i.e., microemusion; column 27, lines 61-64), which can be administered intramuscularly (column 8, lines 48-62), and phosphate is cited as the buffer for pH adjustment, and hyaluronic acid is cited as an example of stabilizing agent, thus hyaluronic acid and phosphate buffer would be included in the formulation for certain

proteins, which meets the criteria of the claimed formulation. Since the claims do not cite the limitation of using smaller needles for injection, it is not necessary for the reference to suggest the inclusion of hyaluronic acid will allow for injection in smaller needles. Furthermore, the formulation containing hyaluronic acid would be expected to have the unexpected and surprising properties of hyaluronic acid.

8. Claims 17, 21, 23, 25-29, 34 and 35 are rejected under 35 U.S.C. 102(e) as being anticipated by Cleland *et al.* (US Patent 6,113,947, filed June 13, 1997).

Cleland *et al.* teach a nerve growth factor (NGF) microencapsulation composition having controlled release characteristics, wherein NGF is dispersed in a polymeric matrix of microspheres, microparticulates and microcapsules (column 2, lines 8-67; column 4, line 62-column 5, line 2; claims 28 and 29) and the microspheres are sieved to about 20-90 microns for injecting intramuscularly (column 19, lines 38-45; column 19, line 63-column 20, line 4; column 23, lines 53-63), and a biodegradable polymer such as a copolymer of lactic acid and glycolic acid (PLGA) is used a polymeric matrix (column 4, lines 24-32, Example 1; claims 25-27). The preferred injectable sustained-release preparation can be formulated with a viscous physiologically acceptable solution including a dispersant such as sodium hyaluronate, a preservative, an isotonizing agent such as NaCl, and a local anesthetic to provide an aqueous suspension (column 19, lines 47-62, claims 17, 21, 23, 34, 35).

In response to the rejection under 35 U.S.C. 102 and 103(a) over Cleland *et al.* alone or in combination with Aldrich catalog, applicants indicates Cleland *et al.* teach the use of hyaluronic acid as a dispersant in a viscous physiologically acceptable solution, and hyaluronic acid is one of the listed dispersants, given the breadth of the list, the

reference cannot be considered to anticipate the present invention, and the unexpected and surprising properties of hyaluronic acid, which allow injection in much smaller needles demonstrates the unobviousness of the claimed invention (page 8 of the response). The response has been fully considered, however, the argument is not found persuasive because the reference indicates to prepare an injection formulation containing the microsphere, a viscous physiologically acceptable solution of a dispersant may be included in the formulation, and hyaluronic acid is as one of the seven specific dispersants cited, which is not very broad considering the breadth of the list, thus the reference anticipates the claimed invention. Since the claims do not cite the limitation of using smaller needles for injection, it is not necessary to consider this issue. Furthermore, the formulation containing hyaluronic acid would be expected to have the unexpected and surprising properties of hyaluronic acid.

9. Claims 17, 21, 23, 25-28 and 34 are rejected under 35 U.S.C. 102(e) as being anticipated by Suzuki *et al.* (US Patent 6,197,326, filed October 14, 1998).

Suzuki *et al.* teach an intra-articular preparation for the treatment of arthropathy, which comprises microcapsules of a biocompatible, high molecular weight substance such as PLGA, homopolymer or copolymer of lactic acid, glycolic acid, caprolactone and others (column 1, lines 45-60; column 2, line 66-column 3, line 30; claims 25-27), and a drug such as steroid agents, cyclosporin (a cyclic peptide; claims 17 and 28), hyaluronic acid (column 3, lines 44-64); and the microcapsules can be administered in the form of injection by suspending it in a dispersion medium, where injection-grade water may be used as the dispersion medium, further, a buffer, an isotonicity (e.g., NaCl; claim 23), and others can be added, particularly a microcapsule-dispersing medium which contains

hyaluronic acid, or chondroitin sulfate or salts thereof is particularly preferred (column 4, line 60-column 5, line 8; claims 21 and 34).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 17, 20, 21, 23, 25-29, 34 and 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cleland *et al.* (US Patent 6,113,947) in view of syringe section (page T515) of Aldrich catalog (1996-1997).

Cleland *et al.* teach a nerve growth factor (NGF) microencapsulation composition having controlled release characteristics, wherein NGF is dispersed in a polymeric matrix of microspheres, microparticulates and microcapsules (column 2, lines 8-67; column 4, line 62-column 5, line 2; claims 28 and 29) and the microspheres are sieved to about 20-90 microns for injecting intramuscularly (column 19, lines 38-45; column 19, line 63-column 20, line 4; column 23, lines 53-63), a biodegradable polymer such as a copolymer of lactic acid and glycolic acid (PLGA) is used a polymeric matrix (column 4, lines 24-32, Example 1; claims 25-27), and the preferred injectable sustained-release preparation can be formulated with a viscous physiologically acceptable solution including a dispersant such as sodium hyaluronate, a preservative, an isotonizing agent such as NaCl, and a local anesthetic to provide an aqueous suspension (column 19, lines 47-62, claims 17, 21, 23, 34, 35). However, Cleland *et al.* does not disclose the type of syringe needle used for injection. The Aldrich catalog shows a 23-gauge syringe needle has an inside

diameter of 0.318 mm (318 microns), which is suitable for injection of the particulate preparation with particle size of 5-200 microns (claim 20). At the time of invention was made, it would have been obvious to one of ordinary skill in the art to administer the microsphere preparation containing NGF to a patient as taught by Cleland *et al.* using a syringe of 23-gauge needle as indicated in the Aldrich catalog because one of ordinary skill in the art would have been motivated to deliver the formulation using the needles having the right gauge, e.g., 23-gauge or smaller. Thus, the combined references result in the claimed invention and was, as a whole, prima facie obvious at the time the claimed invention was made.

11. Claims 22, 30, 31, 36 and 37 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

12. Claims 17, 20, 21, 23, 25-29, 34 and 35 are rejected, and claims 22, 30, 31, 36 and 37 are objected to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

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May 19, 2004

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